Xylene is found in a number of consumer products, including solvents, paints or coatings, and as a blend in gasoline. Mixed xylenes are comprised of 3 isomers: m-xylene, o-xylene, and p-xylene, with the m-isomer predominating. Ethyl benzene is also present in the technical product formulation. Absorbed xylene is rapidly metabolized and is excreted almost exclusively in the urine as methylhippuric acid isomers in humans and as methylhippuric acid isomers and toluic acid glucuronides in animals. In both humans and animals, xylene causes irritation and effects the central nervous system following acute inhalation exposure. No consistent developmental or reproductive effects were observed in the studies found in the available literature. Commercial xylene and all 3 isomers have generally tested negative for genotoxicity. Xylenes are currently not classifiable as to its carcinogenicity by IARC or the U.S. EPA because of inadequate evidence.

The AEGL-1 is based upon the no-effect level was notable discomfort. Only slight eye irritation noted during a 30-minute exposure to 400 ppm mixed xylenes (Hastings et al., 1986). An interspecies uncertainty factor was not applied because the key study used human data. An intraspecies uncertainty factor of 3 was applied because slight eye irritation is caused by a direct effect of the chemical and the response is not expected to vary greatly among individuals ~~the toxic effect (slight irritation) was less severe than that defined for the AEGL-1 tier (notable discomfort)~~. The resulting value of 130 ppm is supported by several other studies, including: a 150 ppm p-xylene exposure resulting in eye irritation in a contact lens wearer (Hake et al., 1981); a 15-minute exposure to 230 ppm mixed xylenes resulting in mild eye irritation and dizziness, but no loss of coordination, in one individual; and a 3-hour exposure to 200 ppm m- or p-xylene (Ogata et al., 1970), a 4-hour exposure to 200 ppm m-xylene (Savolainen et al., 1981), and a 5.5 hour exposure to 200 ppm m-xylene (Laine et al., 1993) all representing no-effect levels for notable discomfort.

The AEGL-2 is based upon the no effect level for the inability to escape. Poor coordination was observed ~~poor coordination resulting~~ when rats were exposed to 1300 ppm mixed xylenes for 4 hours (Carpenter et al., 1975). This concentration represents the threshold for reversible equilibrium disturbances and the no-effect level for the inability to escape. This concentration and endpoint are consistent with the preponderance of available data for 4-hour exposures in rats: the EC_{50} for decreased rotarod performance was 1982 ppm (Korsak et al., 1993); the minimum narcotic concentrations for m-,o-, and p-xylene ranged from 1940-2180 ppm (Molnár et al., 1986); and exposure to 1600 ppm p-xylene resulted in hyperactivity, fine tremor, and unsteadiness (Bushnell, 1989), induced flavor aversion (Bushnell and Peele, 1988), and caused changes in the flash evoked potential suggestive of increased arousal (Dyer et al., 1988). ~~In dogs, exposure to 1200 ppm for 4 hours represented a threshold for eye irritation (Carpenter et al., 1975)~~. An interspecies uncertainty factor of 1 was applied because rats receive a greater systemic dose of inhaled xylene as compared to humans (see Appendix D [PBPK modeling]), and CNS depression results from the parent compound so there should be no substantial difference in response across species to an anaesthetic gas. An intraspecies uncertainty factor of 3 was applied because the MAC (minimum alveolar concentration) for volatile anesthetics should not vary by more than a factor of 2-3-fold among humans. A 3-fold factor is also adequate to account for moderate physical activity during exposure, which would result in ~~greater~~ somewhat more rapid uptake of the chemical.

The AEGL-3 derivation is based upon the no effect level for lethality. Prostration, but no deaths occurred, ~~prostration occurring~~ in all 10 rats exposed for 4 hours to 2800 ppm mixed

xylenes, with recovery occurring within 1 hour of exposure (Carpenter et al., 1975). Although coordination initially remained poor, it returned to normal the following day. ~~This concentration also represents a no-effect level for lethality~~. An interspecies uncertainty factor of 1 was applied because rats receive a greater systemic dose of inhaled xylene as compared to humans (see Appendix D; PBPK modeling]), and a view of the data indicate little difference in interspecies sensitivity to xylene. Lethality data for mice and rats were nearly identical (Cameron et al., 1938; Bonnet et al., 1982), and death was preceded by narcosis that was likely the result of depression of the central nervous system resulting in respiratory arrest. A similar effect has been proposed for humans. Nonlethal effects in both humans and animals are similar in nature and consist primarily of irritation and central nervous system effects. An intraspecies uncertainty factor of 3 was applied because the MAC for volatile anesthetics should not vary by more than a factor of 2-3-fold among humans. A 3-fold factor is also adequate to account for moderate physical activity during exposure, which would result in greater uptake of the chemical.

The two primary effects of concern for xylene are those of irritation and central nervous system effects. Irritation is considered a threshold effect and therefore should not vary over time. The AEGL-1 value based on irritation is therefore not scaled across time, but rather the threshold value is applied to all times.

Data indicate that once steady state is reached, concentration, not duration, is the prime determinant in xylene-induced central nervous system toxicity. Pharmacokinetic modeling in both humans and rats indicate that venous blood concentrations rapidly increase during the first 15 minutes of exposure, followed by minimal increases in blood concentrations with continuing exposure (i.e., increases follow a hyperbolic curve). Likewise, available human data indicate that once the initial increase in blood xylene concentration is reached, blood concentrations level off with increasing exposure duration. Conversely, available human and animal data demonstrate that increasing exposure concentrations correlate with increases in venous blood xylene concentrations. Therefore, the AEGL 2- and -3 values are set equal across time once steady state is approached (starting at approximately 1 hour), while pharmacokinetic modeling was used to extrapolate to exposure durations of 10- and 30-minutes.

The AEGL values should be protective of human health. The AEGL-1 values are consistent with other human studies, and represent a value consistent with exposure concentrations that might result in mild eye irritation. The AEGL-2 levels are protective, especially when considering numerous human studies investigating the effects of exposure to 200 ppm xylene with 20-minute peak exposures to 400 ppm, in some cases additionally combining peak exposures with physical exercise resulting in greater uptake of the chemical, and finding only minimal central nervous system effects. The difficultly in defining an AEGL-2 level for xylene comes from its "all-or-nothing" continuum of toxicity: toxicity ranges from mild irritation to narcosis, with little happening in between. The AEGL-3 levels represent the threshold for narcosis, and are protective as supported by human data demonstrating that exposure to 690 ppm for 15 minutes resulted in lightheadedness/dizziness and a 30 minute exposure to 700 ppm resulted in nausea, vomiting, dizziness or vertigo.

The proposed values are listed in the tables below.

Summary of Proposed AEGL Values for Xylenes [ppm (mg/m³)]						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	130 (560)	130 (560)	130 (560)	130 (560)	130 (560)	No effect level for notable discomfort. Eye irritation in human volunteers exposed to 400 ppm mixed xylenes for 30 minutes (Hastings et al., 1986)
AEGL-2 (Disabling)	990 (4300)	480 (2100)	430 (1900)	430 (1900)	430 (1900)	No effect level for inability to escape. Rats exposed to 1300 ppm mixed xylenes for 4 hours exhibited poor coordination (Carpenter et al., 1975)
AEGL-3 (Lethal)	2100 (9100)	1000 (4300)	930 (4000)	930 (4000)	930 (4000)	No effect level for lethality. Rats exposed to 2800 ppm for 4 hours exhibited prostration followed by a full recovery (Carpenter et al., 1975)

Add footnote for explosion level and asterisk those values exceeding 10% of the LEL

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4.4. Other Relevant Information

4.4.1. Interspecies Differences

Pharmacokinetic data in humans and rats were available for xylene isomers (see section 4.1). A comparison of the blood:air partition coefficients in humans and rats suggest that small rodents will experience greater systemic uptake than humans. The values for the human blood:air partition coefficient are 26.4, 31.9, and 32.5 for m-xylene; 31.1, 35.2, 34.9 for o-xylene; and 37.6, 39.0, and 44.7 for p-xylene (Sato and Nakajima, 1979; Pierce et al., 1996; Gargas et al., 1989), and the values for the rat blood:air partition coefficient are 46.0 for m-xylene; 44.3 for o-xylene, and 41.3 for p-xylene (Gargas et al., 1989).

The interspecies factor is comprised of the pharmacodynamic component as well. A view of the data indicate little difference in interspecies sensitivity to xylene. Lethality data for mice and rats were nearly identical (Cameron et al., 1938; Bonnet et al., 1982). Death was preceded by narcosis and was likely the result of depression of the central nervous system resulting in respiratory arrest. A similar effect has been proposed for humans. Nonlethal effects in both humans and animals are similar in nature and consist primarily of irritation and central nervous system effects.

4.4.2. Intraspecies Differences

All available data point to a 2-3-fold difference in interindividual sensitivity to xylenes.

Xylene acts as an anesthetic (Fang et al., 1996). Studies indicate that children, and particularly infants, are more resistant than adults to the effects of various volatile anesthetics (Gregory et al., 1969; Katoh and Ikeda et al., 1992; Lerman et al., 1983; Matthew et al., 1996; Stevens et al., 1975; LeDez and Lerman, 1987). The susceptibility of individuals of different ages has been extensively studied in the anesthesia literature where the concentrations of various anesthetic gases in the lung which produce "anesthesia" (i.e., lack of movement) have been measured. Values are usually reported as the Minimum Alveolar Concentration (MAC) which produces lack of movement in 50% of persons exposed to that concentration. MAC's for several anesthetic gases have been measured as a function of age. The results consistently show a pattern with maximal sensitivity (lowest MAC) in newborns, particularly prematures, pregnant women, and the elderly. The least sensitive (highest MAC values) occur in older infants, toddlers, and children as compared to normal adults. The total range of sensitivity is 2-3 fold. On the basis of this knowledge, it is not unreasonable to assume that the same 2-3 fold difference in sensitivity among individuals would apply for xylenes.

Exercise has been found to increase alveolar and blood levels of xylenes during exposure (Gamberale et al., 1978; Riihimaki et al., 1979). Using a physiologically-based pharmacokinetic model for m-xylene in humans to assess various interindividual factors in determining the internal dose, Kaneko et al. (1991) reported that physical activity (50W) during a simulated 8-hour exposure to 50 ppm resulted in a 2.5-fold increase in blood concentration when compared to exposure at rest.

Fang et al. (1996) determined the MAC in rats of the individual isomers. The MAC of o-, m-, and p-xylene was 0.00118 ± 0.00009, 0.00139 ± 0.00010, and 00.00151 ± 0.0007 atm, respectively, with a difference of MAC values of less than 30% among the isomers.

4.4.3. Concentration-Exposure Duration Relationship

The two primary effects of xylene exposure are those of irritation and central nervous system effects. Irritation is considered a threshold effect and therefore should not vary over time. An AEGL value based on irritation is therefore not scaled across time, but rather the threshold value is applied to all times.

The central nervous system effects of xylene are attributed to the low molecular weight and lipophilic nature of xylene allowing the solvent to readily cross the blood:brain barrier (see section 4.2). Distribution studies of xylene following inhalation exposures have confirmed high concentrations of xylene in the brain and central and peripheral nervous system immediately after exposure, with elimination often occurring by 1 hour post exposure. The rapid onset of central nervous system effects combined with the transient nature of the xylene-induced nervous system disturbances is likely attributable to direct interaction of the chemical with the central nervous system followed by the rapid elimination of xylene. Based on the above information, the xylene-blood concentration will be a key determinant in central nervous system effects. Pharmacokinetic modeling in both humans and rats indicate that venous blood concentrations rapidly increase during the first 15 minutes of exposure, followed by minimal increases in blood concentrations with continuing exposure (i.e., increases follow a hyperbolic curve) (Tardif et al., 1993; 1995). Likewise, available human data indicate that once the initial increase in blood xylene concentration is reached, blood concentrations level off with increasing exposure duration (see Table 11) (Hake et al., 1981; Savolainen et al., 1980; 1981; 1985b). Conversely, available human and animal data demonstrate that increasing exposure concentrations correlate with increases in venous blood xylene concentrations (Hake et al., 1981; Tardif et al., 1993; Laine et al., 1993). These data indicate that once steady state is reached, concentration, not duration, is the prime determinant in xylene-induced central nervous system toxicity. Therefore, the AEGL values based upon central nervous system effects are set equal across time once steady state is approached (starting at approximately 1 hour), while pharmacokinetic modeling was used to extrapolate to exposure durations of 10- and 30-minutes (see Appendix 2).

TABLE 11. Relationship Between Xylene Exposure Concentration (In Air) and Blood Xylene Concentration in Human Volunteers

Exposure concentration (ppm)	Number of subjects	Time into exposure (h)	Venous blood xylene concentration	Comments	Reference
100*	8	1	18.4 ± 5.3 (μmol/L)	m-Xylene, odor masked with peppermint oil	Savolainen et al., 1980
		1.67	13.3 ± 2.2		
		2	21.6 ± 6.3		
		3	13.4 ± 2.9		
200*	9	0.25	16.6 ± 4.8 (μmol/L)	m-Xylene, odor masked with peppermint oil	Laine et al., 1993
		0.33	17.3 ± 5.5		
		0.67	21.3 ± 5.4		
		2	28.5 ± 5.2		
200	6	1.17	24.9 ± 2.1 (μmol/L)	m-Xylene, odor masked with peppermint oil (<1.0 ppm)	Savolainen et al., 1981
		2.5	26.7 ± 3.4		
		3.75	28.6 ± 3.5		
20	1	1	0.24 (ppm; w/w)	p-Xylene, Subjects were sub-divided into 3 daily groups for 1, 3, or 7.5 hour-long exposures. Males were exposed to 100 ppm for the 1st week (5 days/week), 20 ppm the 2nd week, and 150 ppm the 3rd week. Values reported are for the first exposure day of each new week.	Hake et al., 1981
	2	3	0.41 ± 0.09		
	3	7.5	0.42 ± 0.03		
100	2	1	1.23 ± 0.18		
	2	3	1.65 ± 0.50		
	4	7.5	1.29 ± 0.21		
150	2	1	2.04 ± 0.76		
	2	3	3.18 ± 0.11		
	4	7.5	3.86 ± 0.65		

* Exposure protocol was: 3 hour exposure in the morning, 40 minute break for lunch, followed by exposure for 1 or 3 hours in afternoon. Only values for continuous exposure in the morning session are reported.

5. DATA ANALYSIS AND PROPOSED AEGL-1

5.1. Human Data Relevant to AEGL-1

Exposure to 100, 200 or 400 ppm mixed xylenes for 30 minutes resulted in nonstatistically increased incidences of eye irritation; no nose or throat irritation were noted and no changes in behavioral tests or respiratory measurements were evident (Hastings et al., 1986). That the eye irritation was mild is supported by observation that the number of eye blinks/minute were not affected by exposure. Exposure to 100 or 150 ppm p-xylene for 7.5 hours/day, 5 days/week resulted only in mild eye irritation, most often in one male wearing contact lenses (irritation was noted on the first exposure day) (Hake et al.,1981). No effects on performance tests were observed. Exposure to 110 ppm mixed xylenes for 15 minutes resulted in intermittent, mild throat irritation in 1/6 individuals, while exposure to 230 ppm mixed xylenes for 15 minutes resulted in eye irritation and mild dizziness in 1/7 individuals (Carpenter et al., 1975b).

A number of controlled human exposures reported no effects following exposure to xylenes. Exposure to 100 or 200 ppm m- or p-xylene for 3 or 7 hours did not effect blood pressure, pulse rate, flicker value, or reaction time (Ogata et al., 1970). Olson et al. (1985) found exposure to 70 ppm p-xylene for 4-hours did not effect choice reaction time, simple reaction time, short term memory, heart rate, or subjective symptoms in exposed volunteers. No adverse effects on visual evoked potential, tapping speed, body sway, reaction time, or critical flicker fusion were measured in volunteers exposed to 200 ppm m-xylene for 4 hours (Savolainen et al., 1981; Seppalainen et al., 1983). Body sway, reaction times, and active or quiet sleep were not effected by exposure to 200 ppm for 5.5 hours (Laine et al., 1993).

5.2. Animal Data Relevant to AEGL-1

No effects were observed in dogs exposed to 530 ppm or in rats exposed to 580 ppm mixed xylenes for 4 hours (Carpenter et al., 1975b). Lacrimation in dogs and poor coordination in rats were observed at the next higher exposure concentrations of 1200 ppm and 1300 ppm, respectively (Carpenter et al., 1975b).

5.3. Derivation of AEGL-1

The AEGL-1 is based upon the no-effect level was notable discomfort. Only slight eye irritation noted in the Hastings et al. (1986) study during a 30-minute exposure to 400 ppm mixed xylenes. The effect level for notable discomfort is suggested to be 690 ppm (Carpenter et al., 1975a). At this exposure none of the individuals thought that thires exposure could be tolerated over an 8-hour workday. The Hastings et al. (1986) study was chosen because the exposure was to mixed xylenes as opposed to individual isomers, and the exposure concentration represented a concentration at which an effect was observed, i.e., that of mild eye irritation. An interspecies uncertainty factor was not applied because the key study used human data. An intraspecies uncertainty factor of 3 was applied because slight eye irritation is caused by a direct effect of the chemical and the response is not expected to vary greatly among individuals ~~the toxic effect (slight irritation) was less severe than that defined for the AEGL-1 tier (notable discomfort)~~. Because irritation is considered a threshold effect and should therefore not vary over time, the threshold value is applied to all times. AEGL-1 values are presented in Table 12.

TABLE 12. AEGL-1 Values for Xylenes [ppm (mg/m³)]				
10-minute	30-minute	1-hour	4-hour	8-hour
130 (560)	130 (560)	130 (560)	130 (560)	130 (560)

The 130 ppm value is supported by several other studies, including: the 150 ppm p-xylene exposure resulting in eye irritation in a contact lens wearer (represents sensitive population; Hake et al., 1981); the 15-minute exposure to 230 ppm mixed xylenes resulting in mild eye irritation and dizziness in one individual; and the 3-hour exposure to 200 ppm m- or p-xylene (Ogata et al., 1970), the 4-hour exposure to 200 ppm m-xylene (Savolainen et al., 1981), and the 5.5 hour exposure to 200 ppm m-xylene (Laine et al., 1993), all representing no-effect levels for notable discomfort.

6. DATA ANALYSIS AND PROPOSED AEGL-2

6.1. Human Data Relevant to AEGL-2

One of six or seven individuals noted dizziness during a fifteen minute exposure to 230 ppm (during the last 2 minutes of exposure) or 460 ppm mixed xylenes (starting at the 6th minute and continuing to the end of exposure; same individual), while a 15-minute exposure to 690 ppm mixed xylenes resulted in dizziness/lightheadedness in 4/6 individuals (Carpenter et al., 1975b). In the same study, a 15-minute exposure resulted in eye irritation in 1/7, 4/6 and 4/6 individuals exposed to 230, 460, or 690 ppm mixed xylene, respectively.

6.2. Animal Data Relevant to AEGL-2

Exposure to 1200 ppm or 1300 ppm mixed xylenes for 4 hours represents a threshold for lacrimation in dogs and poor coordination (reversible) in rats, respectively (Carpenter et al., 1975b). The 4-hour m-xylene EC_{50} for decreased rotarod performance in rats was 1982 ppm (Korsak et al., 1993), and the 4-hour minimum narcotic concentrations for the 3 xylene isomers in rats ranged from 1940-2180 ppm (Molnar et al., 1986). Exposure of rats to 1600 ppm p-xylene for 4-hours resulted in hyperactivity, fine tremor, and unsteadiness (Bushnell, 1989), induced flavor aversion (Bushnell and Peele, 1988), and caused changes in the flash evoked potential suggestive of increased arousal (Dyer et al., 1988).

Following 30-minute static exposures in mice, Moser et al., (1985) determined the EC_{50} for decreased performance on the inverted screen test to be 3790 ppm for m-xylene, 3640 ppm for o-xylene, and 2676 ppm for p-xylene, while the EC_{50} for disruption of operant performance was 6176 ppm for m-xylene, 5179 ppm for o-xylene, and 5611 ppm for p-xylene.

6.3. Derivation of AEGL-2

The AEGL-2 is based upon the no effect level for the inability to escape. Poor coordination was observed ~~poor coordination resulting~~ when rats were exposed to 1300 ppm mixed xylenes for 4-hours (Carpenter et al., 1975b). This concentration represents the threshold for reversible equilibrium disturbances and the no-effect level for the inability to escape. This concentration and endpoint are consistent with the preponderance of available data for 4-hour

exposures in rats: the EC_{50} for decreased rotarod performance was 1982 ppm (Korsak et al., 1993); the minimum narcotic concentrations for m-, o-, and p-xylene ranged from 1940-2180 ppm (Molnar et al., 1986); and exposure to 1600 ppm p-xylene resulted in hyperactivity, fine tremor, and unsteadiness (Bushnell, 1989)~~, induced flavor aversion (Bushnell and Peele, 1988), and caused changes in the flash evoked potential suggestive of increased arousal (Dyer et al., 1988). In dogs, exposure to 1200 ppm for 4 hours represented a threshold for eye irritation (Carpenter et al., 1975b)~~. These exposures are effect levels for the inability to escape.

An interspecies uncertainty factor of 1 was applied because rats receive a greater systemic dose of inhaled xylene as compared to humans (see Appendix D [PBPK modeling]), and a view of the data indicate little difference in interspecies sensitivity to xylene (see Section 4.4.1). An intraspecies uncertainty factor of 3 was applied because the MAC (minimum alveolar concentration) for volatile anesthetics should not vary by more than a factor of 2-3-fold among humans. A 3-fold factor is also adequate to account for moderate physical activity during exposure, which would result in greater uptake of the chemical.

Data indicate that once steady state is reached, concentration, not duration, is the prime determinant in xylene-induced central nervous system toxicity (see Section 4.4.3). Therefore, the AEGL-2 values are set equal across time once steady state is approached (starting at approximately 1 hour), while pharmacokinetic modeling was used to extrapolate to exposure durations of 10- and 30-minutes (see Appendix B).

AEGL-2 values are presented in Table 13.

TABLE 13. AEGL-2 Values for Xylenes [ppm (mg/m^3)]

10-minute	30-minute	1-hour	4-hour	8-hour
990 (4300)	480 (2100)	430 (1900)	430 (1900)	430 (1900)

The human data reported by Carpenter et al. (1975b) were not used for the AEGL-2 derivation because the exposure duration was for only a short time (15 minutes) and because it not consistent with the preponderance of human data from other controlled human exposures. If one were to use the highest exposure concentration (690 ppm which resulted in eye irritation and dizziness in 4/6 individuals; threshold for equilibrium effects) and apply the intraspecies uncertainty factor of 3, one obtains a value of 230 ppm. This concentration is supposed to represent a concentration at which exposed individuals could experience irreversible or other serious, long-lasting adverse health effects, or have an impaired ability to escape. However, a number of studies demonstrate that only minor sensory irritation is observed ~~this concentration has no adverse effects upon exposed individuals: no adverse effects were observed~~ following exposure to 100 or 200 ppm m- or p-xylene for 3 or 7 hours (Ogata et al., 1970); 200 ppm m-xylene for 4 hours (Savolainen et al., 1981; Seppalainen et al., 1985), or 200 ppm for 5.5 hours (Laine et al., 1993).

Additionally, numerous human studies investigated the effects of exposure to: 200 ppm m-xylene with 20 minute peaks of 400 ppm (Seppalainen et al., 1989; 1991; Laine et al., 1993;

Savolainen and Linnavuo, 1979); 135 ppm m-xylene with 20 minute peaks of 400 ppm (Savolainen et al., 1984; 1985a; 1985b); or 140 ppm m-xylene with 10 minute peaks of 400 ppm (Riihimaki and Savolainen, 1980; Savolainen and Riihimaki, 1981). The studies also combined peak exposures with exercise, thereby increasing the uptake of the chemical. These studies found either no effect; or ~~reported~~ only minimal central nervous system effects.

7. DATA ANALYSIS AND PROPOSED AEGL-3

7.1. Human Data Relevant to AEGL-3

Morley et al. (1970) reported the cases of 3 individuals exposed to approximately 10,000 ppm xylene for approximately 18 hours. One individual died, while the other two individuals were found unconscious but experienced a full recovery.

7.2. Animal Data Relevant to AEGL-3

Two cats exposed to 9500 ppm mixed xylenes exhibited central nervous system effects followed by death 2 hours into the exposure (Carpenter et al., 1975b). In rats, 4-hour LC_{50}s values for mixed xylenes have been reported as 6350 ppm (Hine and Zuidema, 1970), 6011 ppm (Carpenter et al., 1975b), and 11,000 ppm (Lundberg et al., 1986), and for p-xylene as 4645 ppm (Harper et al., 1975). Six-hour LC_{50} values for the m-, o-, and p-isomers were 5984, 4330, and 4591 ppm in rats, respectively, and 5267, 4595, and 3907 ppm in mice, respectively (Bonnet et al., 1979; 1982).

A no-effect level for death in rats following exposure to mixed xylenes for 4 hours was 2800 ppm (Carpenter et al., 1975b). Clinical signs observed during exposure to 2800 ppm included prostration between 2-3.5 hours into the exposure. Recovery occurred within 1-hour post exposure, but coordination remained poor until the following day. At the next lower concentration of 1300 ppm, poor coordination was noted 2 hours into the exposure, with coordination returning to normal after the exposure. Molnar et al. (1986) reported 4-hour minimum narcotic concentrations of 2100, 2180, and 1940 ppm for the m-, o-, and p-xylene isomers, respectively.

RD_{50} values in mice were 1467 ppm for o-xylene (De Ceaurriz et al., 1981), 1361 ppm for m-xylene (Korsak et al., 1993), and 2440 ppm for mixed xylenes (Korsak et al., 1988). It should be noted, however, that Korsak et al. (1993; 1988) did not use the recommended strain of mice.

7.3. Derivation of AEGL-3

The AEGL-3 derivation is based upon the no effect level for lethality. Prostration, but no deaths occurred, ~~prostration occurring~~ in all 10 rats exposed for 4 hours to 2800 ppm mixed xylenes, with recovery occurring within 1 hour of exposure (Carpenter et al., 1975b) Although coordination initially remained poor, it returned to normal the following day. ~~This concentration also represents a no-effect level for lethality.~~

An interspecies uncertainty factor of 1 was applied because rats receive a greater systemic dose of inhaled xylene as compared to humans (see Appendix D [PBPK modeling]), and a view of

the data indicate little difference in interspecies sensitivity to xylene (see Section 4.4.1). An intraspecies uncertainty factor of 3 was applied because the MAC (minimum alveolar concentration) for volatile anesthetics should not vary by more than a factor of 2-3-fold among humans. A 3-fold factor is also adequate to account for moderate physical activity during exposure, which would result in greater uptake of the chemical.

Data indicate that once steady state is reached, concentration, not duration, is the prime determinant in xylene-induced central nervous system toxicity (see Section 4.4.3). Therefore, the AEGL-3 values are set equal across time once steady state is approached (starting at approximately 1 hour), while pharmacokinetic modeling was used to extrapolate to exposure durations of 10- and 30-minutes (see Appendix B).

AEGL-3 values are presented in Table 14.

TABLE 14. AEGL-3 Values for Xylenes [ppm (mg/m^3)]

10-minute	30-minute	1-hour	4-hour	8-hour
2100 (9100)	1000 (4300)	930 (4000)	930 (4000)	930 (4000)

Available data indicated that these values should be protective of human health. A 15-minute exposure to 690 ppm for 15 minutes resulted in eye irritation and dizziness and/or lightheadedness (Carpenter et al., 1975b), and a 30 minute exposure to concentrations as high as 700 ppm xylene resulted in headache, nausea, vomiting, dizziness or vertigo, eye irritation, or nose or throat irritation (Klaucke et al., 1982).

8. SUMMARY OF PROPOSED AEGLs

8.1. AEGL Values and Toxicity Endpoints

The proposed AEGL values for xylenes are summarized in Table 15.

TABLE 15. Summary/Relationship of AEGL Values [ppm(mg/m^3)]

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	130 (560)	130 (560)	130 (560)	130 (560)	130 (560)
AEGL-2 (Disabling)	990 (4300)	480 (2100)	430 (1900)	430 (1900)	430 (1900)
AEGL-3 (Lethal)	2100 (9100)	1000 (4300)	930 (4000)	930 (4000)	930 (4000)

APPENDIX B: Time-Scaling Calculations

Derivation of AEGL-2 (10 minutes and 30 minutes)

Because the key study for the AEGL-2 derivation is a study with a 4-hour exposure duration, extrapolation to shorter time periods was necessary. It was decided to use a toxicokinetic approach to calculate AEGL-2 values for 10 minutes and for 30 minutes.

The following assumptions were made:

(i) the toxicological endpoint and the intensity of toxicological effect should be the same as observed after administration of 430 ppm for 4 hours
(ii) it is the concentration and not the amount of the substance (AUC) which is responsible for the effect, qualitatively and quantitatively
(iii) the data from kinetic studies in human volunteers (see Table 11, page 37) are appropriate for further kinetic calculations
(iv) the data of m-xylene were used to represent the mixture of all xylenes
(v) the kinetics of m-xylene are linear in the concentration/dose range which is under consideration.

Calculations: The data of three studies were used. The external concentration in the air multiplied by inhalation volume and frequency was used as input rate. A one-compartment body model described the data appropriately. The calculations were done using NONMEM program. After the concentration at 4 hours was calculated, the input rate to reach this concentration with 10 minutes and 30 minutes, respectively, was estimated. As we assumed inhalation volume and frequency being constant, the external air concentration was obtained by eliminating the constant.

The outcome of the calculations was as follows: k which is the first order elimination constant was 2.74/ hour; the corresponding half life is 0.25 hours. The concentration at 4 hours was 6.5 ± 10 mmol/L (mean ±2 SD) for 430 ppm. The external air concentration to reach this concentration within 10 minutes is 1165 ±180 ppm (mean ±2 SD) and within 30 minutes is 570±87.5 (mean±2 SD).

Calculating the lower boundary value for 2 SD results in
10 min: 985 ppm
30 min: 482.5 ppm

Calculating the lower boundary value for 3 SD results in
10 min: 896 ppm
30 min: 438.4 ppm
Please see Figure.

conc (mmol/L)	65 (mean)	55 (-2 SD)	50 (-3 SD)
10 min	1165 ppm	985 ppm	896 ppm
30 min	570 ppm	483 ppm	438 ppm

Derivation of AEGL-3 (10 minutes and 30 minutes)

Because the key study was a study with a 4-hour exposure duration, extrapolation to shorter time periods was necessary. It was decided to use a toxicokinetic approach to calculate AEGL-3 values for 10 and for 30 minutes.

The following assumptions were made:

(i) the toxicological endpoint and the intensity of toxicological effect should be the same as observed after administration of 930 ppm for 4 hours
(ii) it is the concentration and not the amount of the substance (Auc) which is responsible for the effect, qualitatively and quantitatively
(iii) the data from kinetic studies in human volunteers (see Table 11, page 37) are appropriate for further kinetic calculations
(iv) the data of m-xylene were used to represent the mixture of all xylenes
(v) the kinetics of m-xylene are linear in the concentration/dose range which is under consideration.

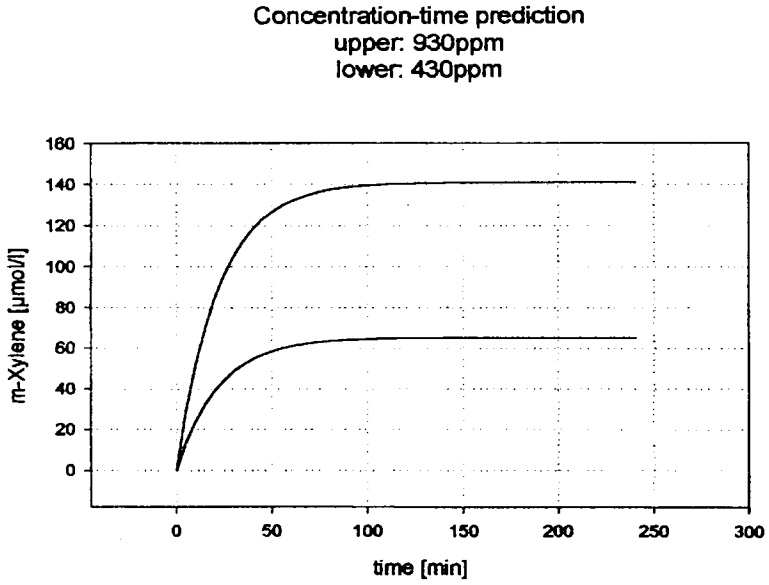
Calculations: The data of three studies were used. The external concentration in the air multiplied by inhalation volume and frequency was used as input rate. A one-compartment body model described the data appropriately. The calculations were done using NONMEM program. After the concentration at 4 hours was calculated, the input rate to reach this concentration within 10 minutes and 30 minutes, respectively, was estimated. As we assumed inhalation volume and frequency being constant, the external air concentration was obtained by eliminating the constant.

The outcome of the calculations was as follows: k which is the first order elimination constant was 2.74/hour; corresponding half life is 0.25hours. The concentration at 4 hours. was 141 ± 25 mmol/L (mean ± 2 SD) for 930 ppm. The external air concentrations to reach this concentration within 10 minutes is 2526 ± 455 ppm (mean ± 2SD) and within 30 minutes is 1237 ± 221 ppm (mean ± 2 SD).

Calculating the lower boundary value for 2 SD results in
10 min: 2071 ppm
30 min. 1016 ppm

Calculating the lower boundary value for 3 SD results in
10 min: 1790 ppm
30 min: 963 ppm
Please see Figure.

conc (mmol/L)	141 (mean)	116 (-2 SD)	103.5 (-3 SD)
10 min	2526 ppm	2071 ppm	1790 ppm
30 min	1237 ppm	1016 ppm	963 ppm


Concentration-time prediction
upper: 930ppm
lower: 430ppm
m-Xylene [µmol/l]
160
140
120
100
80
60
40
20
0
0
50
100
150
200
250
300
time [min]

APPENDIX C: Derivation Summary for Xylene AEGLs

ACUTE EXPOSURE GUIDELINES FOR XYLENES CAS Reg. No. 1330-20-7 DERIVATION SUMMARY

AEGL-1 VALUES				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
130 ppm	**130 ppm**	**130 ppm**	**130 ppm**	**130 ppm**

Key Reference: Hastings, L., Cooper, G.P., and Burg, W. 1986. Human sensory response to selected petroleum hydrocarbons. In: MacFarland, H.N. ed. Advances in Modern Environmental Toxicology. Vol. VI. Applied Toxicology of Petroleum Hydrocarbons. Princeton, NJ: Princeton Scientific Publishers, pp. 255-270.

Test Species/Strain/Number: Volunteer human male

Exposure Route/Concentrations/Durations: Subjects were exposed by inhalation via an olfactometer delivery hood to 0, 100, 200, or 400 ppm mixed xylene for 30 minutes

Effects: Mild eye irritation reported by 56, 60, 70, and 90% of subjects exposed to 0, 100, 200, or 400 ppm mixed xylene, respectively; no effects observed on behavioral test results

Endpoint/Concentration/Rationale: Mild eye irritation was noted by 90% of the subjects exposed to 400 ppm

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1 - human data used
Intraspecies: 3 - the toxic effect (slight irritation) was less severe than that defined for the AEGL-1 tier (notable discomfort).

Modifying Factor: NA (1)

Animal to Human Dosimetric Adjustment: NA - human data used

Time Scaling: Irritation is considered a threshold effect and therefore should not vary over time. The AEGL-1 value based on irritation is therefore not scaled across time, but rather the threshold value is applied to all times.

Data Adequacy: This was an acceptable study, but could have been improved had the number of volunteers been reported. However, the data are consistent with other human studies, and represent a value consistent with exposure concentrations that might result in mild eye irritation.

AEGL-2 VALUES				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
990 ppm	**480 ppm**	**430 ppm**	**430 ppm**	**430 ppm**

Key Reference: Carpenter, C.P., Kinkead, E.R., Geary, D.L. Jr., Sullivan, L.J., and King, J.M. 1975. Petroleum hydrocarbon toxicity studies. V. Animal and human response to vapors of mixed xylene. Toxicol. Appl. Pharmacol. 33: 543-58.

Test Species/Strain/Number: 10 male albino rats (Harlan-Wistar strain) approximately 5 weeks old/group

Exposure Route/Concentrations/Durations: Rats were exposed by inhalation to 580, 1300, 2800, 4000, or 9000 ppm mixed xylene for 4 hours

Effects:

Conc.(ppm)	Mortality	Other effects
580	0/10	none observed
1300	0/10	poor coordination after 2 hours, returned to normal
2800	0/10	irritation; all rats prostrate between 2-3.5 hours recovered within 1 hr, coordination returned to normal next day
6000	4/10	rats prostrate within 30 minutes; all survivors prostrate but recovered promptly
9900	10/10	none stated

Endpoint/Concentration/Rationale: Exposure to 1300 ppm for 4 hours resulted in poor coordination

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1 - An interspecies uncertainty factor of 1 was applied because rats receive a greater systemic dose of inhaled xylene as compared to humans.
Intraspecies: 3 - The MAC (minimum alveolar concentration) for volatile anesthetics should not vary by more than a factor of 2-3-fold among humans. A 3-fold factor is also adequate to account for moderate physical activity during exposure, which would result in greater uptake of the chemical.

Modifying Factor: NA (1)

Animal to Human Dosimetric Adjustment: NA

Time Scaling: Data indicate that once steady state is reached, concentration, not duration, is the prime determinant in xylene-induced central nervous system toxicity. Therefore, the AEGL-2 values are set equal across time once steady state is approached (starting at approximately 1 hour), while pharmacokinetic modeling was used to extrapolate to exposure durations of 10- and 30-minutes.

Data Adequacy: This was a well-designed and conducted study. The data are supported by numerous other studies in rats, as well as a study in dogs. The AEGL-2 levels are protective of human health, especially when considering numerous human studies investigated the effects of exposure to 200 ppm xylene with 20-minute peak exposures to 400 ppm, in some cases additionally combining peak exposures with physical exercise resulting in greater uptake of the chemical, and found only minimal central nervous system effects.

AEGL-3 VALUES				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
2100 ppm	**1000 ppm**	**930 ppm**	**930 ppm**	**930 ppm**

Key Reference: Carpenter, C.P., Kinkead, E.R., Geary, D.L. Jr., Sullivan, L.J., and King, J.M. 1975. Petroleum hydrocarbon toxicity studies. V. Animal and human response to vapors of mixed xylene. Toxicol. Appl. Pharmacol. 33: 543-58.

Test Species/Strain/Number: 10 male albino rats (Harlan-Wistar strain) approximately 5 weeks old/group

Exposure Route/Concentrations/Durations: Rats were exposed by inhalation to 580, 1300, 2800, 4000, or 9000 ppm mixed xylene for 4 hours

Effects:

Conc.(ppm)	Mortality	Other effects
580	0/10	none observed
1300	0/10	poor coordination after 2 hours, returned to normal
2800	0/10	irritation; all rats prostrate between 2-3.5 hours recovered within 1 hr, coordination returned to normal next day
6000	4/10	rats prostrate within 30 minutes; all survivors prostrate but recovered promptly
9900	10/10	none stated

Endpoint/Concentration/Rationale: Exposure to 2800 ppm for 4 hours resulted in prostration followed by full recovery

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1 - An interspecies uncertainty factor of 1 was applied because rats receive a greater systemic dose of inhaled xylene as compared to humans.
Intraspecies: 3 - The MAC (minimum alveolar concentration) for volatile anesthetics should not vary by more than a factor of 2-3-fold among humans. A 3-fold factor is also adequate to account for moderate physical activity during exposure, which would result in greater uptake of the chemical.

Modifying Factor: NA (1)

Animal to Human Dosimetric Adjustment: NA

Time Scaling: Data indicate that once steady state is reached, concentration, not duration, is the prime determinant in xylene-induced central nervous system toxicity. Therefore, the AEGL- 3 values are set equal across time once steady state is approached (starting at approximately 1 hour), while pharmacokinetic modeling was used to extrapolate to exposure durations of 10- and 30-minutes.

Data Adequacy: This was a well-conducted study. The AEGL-3 levels are supported by human data demonstrating that exposure to 690 ppm for 15 minutes resulted in lightheadedness/dizziness and a 30 minute exposure to 700 ppm resulted in nausea, vomiting, dizziness or vertigo.